The results of a meta-analysis of 19 clinical trials provide evidence for a beneficial, statistically significant as well as clinically relevant efficacy of diacerein on pain and the functional status in patients suffering from hip and knee OA [19]. The number of patients inluded in this meta-analysis, namley, 1328 diacerein-treated patients and 1309 patients in the comparator groups (placebo or NSAID) gives the basis for well founded conclusions to be drawn from this investigation.

It could be shown that diacerein was superior to placebo and as effective as NSAIDs with respect to the reduction of pain as well as to the improvement of function which are considered to constitute major response criteria in OA during the treatment period. As functionality is highly dependent upon pain its reduction relates directly to the improvement of the functional status.

Considering the pain relief results, one has to keep in mind that no complete withdrawal of analgesic medication was possible during the investigations analyzed within this meta-analysis. In most of the trials, acetaminophen, which can be also seen as an appropriate treatment of moderate OA, was allowed as additional medication.

In addition the results of this meta-analysis give a proof for the carry over effect, SYSADOA are postulated to exert, concerning pain assessed by VAS.

The most common side effects of diacerein are related to the gastrointestinal tract like abdominal pain or diarrhoe. Moreover, change of the urine colouration, pruritus and skin rash occurred within the clinical trials. All these adverse events were reversible and not life threatening. In France, over a period of 11 years (from September 1994 to November 2005) and with more than 14 million prescriptions of DIA, only 9 cases of cardiovascular adverse events with DIA were spontaneously reported. Patient tolerability assessments revealed the superiority of placebo over diacerein with no differences between diacerein and NSAIDs. Given the meta-analytic results obtained here, a trial powered to ultimately prove the usefulness of diacerein as a symptom-modifying or even disease-modifying drug in osteoarthritis can be expected to give similar results.

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GLUCOSAMINE

Karel Pavelka

Despite several new studies [1,2] several meta-analysis and new Cochrane analysis, discussion on efficacy of glucosamine in both symptomatic and structural modification of OA continues.

Why? Firstly, there are general problems with evaluation of drugs in OA. There is high placebo response, problem with rescue medication and other therapies. We definitively need better study designs and outcome measures.

Secondly there is a problem with the drug. Is glucosamine sulfate equally effective as glucosamine hydrochloride? New studies

have clearly documented higher bioavailibility of glucosamine sulfate then of glucosamine hydrochloride.
Thirdly there is need for standardization of radiographic methods and validation of new methods like MRI for easier and more precise proof of potential retarding effect of drug on cartilage degeneration.
Fourthly we need to know more, about exact mechanism of action of GS. New knowledge of effect of GS on inhibition of the cytokine intracellular signalling pathway, namely of the activation of NF – kB is an example of this.
Fifthly there are differences in regulatory aspects of glucosamine being registered as drug in Europe and nutritient in US that again complicates situation.
Conclusions: Overall studies support efficacy of glucosamine. Discrepancies may relate to product variation. NIH study will add further to current information.

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CHONDROITIN SULPHATE

Beat A. Michel

Background: Chondroitin Sulphate (CS) is widely used throughout the world for the treatment of osteoarthritis (OA). EULAR recommendations include CS as a symptomatic slow acting drug for OA (SYSADOA) in the management of both knee and hip OA (strength of recommendation according to category 1 evidence). However, many controversies remain to this date.
Evidence of symptomatic efficacy: Meta-analyses have shown, that effect sizes regarding the symptomatic efficacy of CS in published studies are high (reaching 0.8). However, effect sizes are diminished when only high quality and large trials are considered. For both pain and functional outcomes effect sizes were relatively consistent.
Not all studies have found significant symptomatic efficacy. Whether this finding is based on a floor effect (very low baseline values), patient selection, large response within the placebo group or other factors is open to debate.
Structure modifying effect: Two large studies have examined the structure modifying effect of CS in OA of the knee. Both studies, one one-center study and one multi-center European study have found significant differences in the progression of disease between treated and placebo groups over two years. Both studies used flexed radiographic views to assess the outcome parameters of joint space narrowing. In both studies automatic reading of digitized radiographs were used. A further NIH-sponsored large trial will be analysed within the next months with regard to structure modification.
Open questions: Many issues regarding the treatment of CS are still open and need appropriate assessment: Absorption via the gastrointestinal tract; exact way of action leading to symptomatic relief and/or structure modification; optimal dosage; optimal origin of substance; schedule of treatment over time; efficacy in the treatment of OA of hands and spine.
Conclusion: Overall CS appears to possess symptomatic slow onset efficacy in OA of the hip and knee, although the effect sizes may be smaller than suggested by the publications available. Also current data support structure modifying effects of CS in OA of the knee. However, much more work is needed to understand the exact mechanisms of action all the way from the intake of the substance to the suggested outcomes. The fact, that CS is very well tolerated, will further stimulate ongoing work in this field.